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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,385	05/16/2005	Franz Grus	2005-0532A	6519

513 7590 06/02/2006

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EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/531,385	GRUS ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *12-15 and 19-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 16-18* is/are rejected.

7)☒ Claim(s) *1, 10, 17-18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-18 in the reply filed on May 12, 2006 is acknowledged. The election of the species of **retinal antigens** as the species of ocular antigens and of **Western blot** as the assay format is further acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicant indicated that claims 15-18 read on the elected species of **Western blot assay**. However, the Examiner has determined that claim 15, which refers to a bead-based assay and to "SELDI-TOF", does not read on the elected species.

3. Claims 12-15 and 19-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species and inventions, there being no allowable generic or linking claim.

4. Claims 1-26 are pending in the application, with claims 1-11 and 16-18 currently under examination.

Claim Objections

5. Claim 1 is objected to because it recites "body fluids" of an individual, while claims 4-6 refer to "the body fluid". It would seem that only one body fluid is being sampled from an individual, such that the claim should read "a body fluid" rather than "body fluids".

6. Claim 10 is objected to because the abbreviations "ELISA" and "RIA" should be accompanied by the full terms when they first appear in the claims.

7. Claim 17 is objected to because it would seem that the autoantibodies referred to in the claim are those previously recited in claim 1. For clarity, it is suggested that claim 17 refer to "the autoantibodies" or "said autoantibodies".

8. Claim 18 is objected to because of the following informalities: the word "severeness" should read --severity--.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-11 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting autoantibodies in serum samples, does not reasonably provide enablement for detecting autoantibodies in all body fluids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention relates to a method for diagnosis of glaucoma in which autoantibodies that are directed against ocular antigens are detected in a patient, and compared to patterns of autoantibodies from positive and negative controls (glaucoma patient and healthy controls, respectively). In particular, the specification discloses experiments in which extracts of retinas were prepared by homogenization of bovine retinas. The retinal antigens in the extracts were separated according to their molecular weights as bands on a gel by SDS-PAGE and then blotted onto nitrocellulose membranes. The membranes were then exposed to patient serum;

autoantibodies in the serum that bound to ocular antigens on the membranes were detected by Western blot techniques using a labeled secondary antibody (see p. 12-16, "Western blots"). Detection of signal at a particular band on the membrane indicated that the serum sample contained an autoantibody that bound to the ocular antigen at that particular size band. Such autoantibody-antigen binding data was determined for many different antigens/size bands (see p. 15, lines 27-31). Data were collected in this way from the serum of healthy individuals and from the serum of glaucoma patients. The specification discloses that there was a significant difference between the patterns of glaucoma patients as compared with normal controls (see p. 14, lines 19-26 in particular). A training algorithm was constructed (p. 15) in order to determine whether diagnosis of glaucoma could be achieved based on autoantibody pattern data. In the specification, data from 42 different antigens/size bands was used to create such an algorithm, and this data permitted 83.5% of glaucoma patients and 85.2% of healthy subjects to be correctly classified (p. 15, line 27 to p. 16, line 6).

The specification discloses that autoantibodies against ocular autoantigens may be detected in body fluids from an individual, including serum, tears, saliva, urine, aqueous humor, or vitreous humor (p. 6, line 33 to p. 7, line 3; and claims 4-6). However, the specification provides data only for serum (p. 12, line 16). There are no working examples in which autoantigens were detected in any of the other body fluids claimed.

The prior art teaches that antibodies are normally found in serum (see Janeway et al., Immunobiology: The Immune system in Health and disease, Fourth Edition, 1999, Elsevier Science Ltd/Garland Publishing, New York, NY, at p. 34). Furthermore, the prior art also teaches that measurements of autoantibodies can be of very different diagnostic value depending on the

body fluid sample in which the autoantibodies are measured. For example, Baldas et al. ("Testing for Anti-Human Transglutaminase Antibodies in Saliva Is Not Useful for Diagnosis of Celiac Disease" *Clinical Chemistry* **50** (2003), 216-219) teach that anti-transglutaminase may be detected in both serum and in saliva (see in particular Figure 1), but that saliva was not a good source of autoantibodies for diagnostic purposes (see the abstract and p. 218), such that measurement of autoantibodies in saliva was not useful for diagnosis (the title). Thus, with analogy to the autoantibody of Baldas et al., the specification's disclosure that autoantibodies in serum may be used in diagnosis is not sufficient to enable one skilled in the art to diagnose glaucoma based on the levels of autoantibodies in all body fluids including tears, saliva, urine, aqueous humor, or vitreous humor.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-11 and 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claim 1 recites the limitation "the autoantibody pattern". There is insufficient antecedent basis for this limitation in the claims.

14. Claim 1 recites that an autoantibody pattern from an individual is "**correlated with corresponding patterns**" of healthy individuals and of glaucoma patients. The recitation of correlation of autoantibody patterns is vague and indefinite. The term "correlated" is not specifically defined in the specification, such that it is unclear what steps are actually being

performed--are the patterns compared? Grouped or presented together? The use of this terminology does not allow for the metes and bounds of the claims to be adequately identified.

15. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step in which glaucoma is diagnosed. The method recites that autoantibody patterns are "correlated", but does not clearly set forth a step in which a diagnosis of glaucoma is made on the basis of the correlation. The claim also does not state, for example, whether a diagnosis would be made if the pattern were statistically the same/different relative to the healthy control or glaucoma control patients.

16. Claim 2 recites "a mixture of **such** antigens". The phrase "such" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

17. Claim 16 recites the limitation "the technique" in line 1. There is insufficient antecedent basis for this limitation in the claim.

18. Claim 16 refers to a technique that is "based on...digital image detection, processing, and analysis". The terms "processing" and "analysis" are vague and indefinite, such that one skilled in the art would not be reasonably apprised of the scope of a technique. The use of the terminology "based on" also renders the claim indefinite, since the scope of techniques "based on" the recited steps is unclear.

19. Claim 18 recites the limitations "the change" and "the progression" in lines 1 and 2, respectively. There is insufficient antecedent basis for these limitations in the claim.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 1-6, 10-11, and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Joachim et al. ("Analysis of Autoantibody Repertoires in Patients with Glaucoma," Meeting Abstract, Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, USA, May 5-10, 2002, Applicant's Information Disclosure statement).

Joachim et al. teach a method in which autoantibodies against retinal antigens were detected in the sera of glaucoma patients and healthy subjects. The autoantibodies were detected and measured by Western blot and subsequently analyzed by multivariate statistical techniques and artificial neural networks. The staining patterns of autoantibodies for each individual was digitized, grouped together, and analyzed by multivariate statistical techniques and artificial neural networks. Joachim et al. further teach that a difference in the autoantibody patterns of patients with primary open angle glaucoma was observed relative to the patterns of healthy controls.

Although Joachim et al. do not specifically recite that the method is used to diagnose glaucoma, the teaching is anticipatory since Joachim et al. teach all active method steps recited in claim 1.

With respect to claims 2-3, Joachim et al. teach that autoantibodies were specific for *retinal antigens*.

With respect to claims 4-6 and 17, Joachim et al. teach that *serum* was analyzed for the presence of autoantibodies.

Claim Rejections - 35 USC § 103

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

24. Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Joachim et al. in view of Grus et al. ("Computer-supported analysis (MegaBlot) of allopurinol-induced changes in the autoantibody repertoires of rats suffering from experimental lens-induced uveitis" *Electrophoresis* **18** (1997) 516-519).

Joachim et al. is as discussed above, which teaches methods in which autoantibody patterns (repertoires) of patients with glaucoma are compared to those of normal controls.

However, the reference is an abstract and fails to explicitly state what number of autoantibodies made up the patterns.

Grus et al. teach that normal sera contain complex repertoires of naturally occurring autoantibodies, such that pathogenetically relevant autoantibodies may be eclipsed by such natural autoantibodies (p. 516, left column). In order to address this problem, Grus et al. teach a multivariate approach a quantitative immunoblot technique ("Megablot") in which several hundred autoantigens are screened simultaneously for corresponding autoantibodies (see the abstract and p. 516, "Introduction," in particular). Grus et al. teach that this multivariate approach allows for a quantitative analysis of whether differences between groups are statistically significant in disease (see in particular Figure 1; p. 517, right column, the second paragraph; and p. 518-519, "Discussion"), and may also be used to detect and monitor changes in the autoantibody repertoire during treatment.

Therefore, it would have been obvious to one of ordinary skill in the art to employ the method of Grus et al, in which several hundred autoantigens are simultaneously screened, in order to allow for quantitative comparison of normal and glaucoma groups, to prevent naturally occurring autoantibodies from masking changes in pathogenetically relevant ones, and/or to allow for monitoring of changes in pathogenetically relevant autoantibodies during treatment of glaucoma.

25. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Joachim et al. in view of Maruyama et al. ("Clinical Roles of Serum Autoantibody against Neuron-Specific Enolase in Glaucoma Patients" *Tohoku J. Exp. Med.* (July 2002), **197**, 125-132).

Joachim et al. is as discussed above, which teaches detecting and comparing autoantibody patterns in glaucoma. However, the reference fails to specifically teach that changes in autoantibody patterns over time were used to assess the progression and/or severity of glaucoma.

Maruyama et al. teach detection of an autoantibody against a retinal antigen (autoantibody against neuron-specific enolase), in which the autoantibody titers in glaucoma patients with and without visual field deterioration were compared in order to evaluate the clinical role of the autoantibody in relation to clinical findings (see in particular the abstract; p. 126, right column, the first full paragraph; p. 130, left column, the first paragraph). Glaucoma with visual field deterioration would be considered to be more severe than glaucoma without such deterioration. Maruyama et al. found that the autoantibody titers were relatively higher in glaucoma with visual field deterioration than in patients without it (see also p. 131, left column). In addition, Maruyama et al. found that the autoantibody titers were observed to change with advancing glaucoma stages and/or deteriorating glaucomatous visual field losses (p. 130, left column and Figure 2). Maruyama et al. conclude that detection of the autoantibody may be used in diagnosis and to monitor glaucoma progression (p. 131, right column).

Therefore, it would have been obvious to one of ordinary skill in the art to assess changes in autoantibody patterns over time, as taught by Maruyama et al., in the method of detecting autoantibody patterns of Joachim et al. in order to monitor glaucoma progression. One would have a reasonable expectation of success because Maruyama et al. found that levels of one retinal autoantibody changed with glaucoma severity and with disease progression; and retinal autoantibodies were those studied in Joachim et al.

Conclusion

26. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Romano et al. ("Anti-rhodopsin antibodies in sera from patients with normal-pressure glaucoma" *Invest Opthalmol Vis Sci* **36** (1995) 1968-75) found that autoantibodies directed against retinal antigens, including rhodopsin, were found at higher titers in glaucoma patients and suggest the use of serum autoantibodies in diagnosis of glaucoma (see in particular p. 1973-1974).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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